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Study protocol

Study title

Investigating biases in observational studies of inhaled corticosteroids and the risk of COVID-19-related outcomes.

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A. Lay summary

Inhaled corticosteroids (ICS) are anti-inflammatory medications commonly used as routine medications in asthma and chronic obstructive pulmonary disease (COPD). At the beginning of the COVID-19 pandemic, it was thought that people with asthma or COPD might be at a higher risk of severe COVID-19 but this was not observed early in the pandemic. It was not clear why, but it was suggested that lung disease, patients' behaviour or their treatment may have a protective effect against severe COVID-19.

In this study, we will examine the association between ICS use and SARS-CoV-2 infection, COVID-19 hospital admission, and COVID-19 death among people who have either asthma or COPD. We will also examine, using a set of methods called quantitative bias analysis, how systematic biases may have affected any observed association between ICS use and COVID-19 outcomes. This could include addressing errors relating to e.g., undetected COVID-19 cases, or systematic differences between patients who were prescribed ICS and those who were not.

This project will help understand the role of ICS in COVID-19 and the systematic biases that can affect observational studies of medications and COVID-19. This will in turn help researchers to conduct more reliable observational studies, and more robust results and interpretations of observational drug studies during a pandemic.

B. Technical summary

Inhaled corticosteroids (ICS) are anti-inflammatory drugs widely used as regular maintenance medications in asthma and chronic obstructive pulmonary disease (COPD). At the beginning of the COVID-19 pandemic, there was interest in ICS as potential disease-modifying drugs in COVID-19. Several observational studies investigated the effects of ICS on COVID-19 outcomes but found inconsistent results that may be affected by biases.

The aim of this study is to investigate the effects of ICS at different stages of the COVID-19 disease pathway among patients with asthma or COPD, and apply methods of quantitative bias analysis (QBA) to these effect estimates to account for potential biases arising in these estimates of association.

This study will use cohorts of patients with asthma and COPD, respectively, to investigate the association between ICS use compared to use of a non-ICS active comparator and SARS-CoV-2 infection, COVID-19 hospitalisation, and COVID-19 death. All analyses will be conducted separately for an asthma and COPD cohort, and for the first and second wave of COVID-19. CPRD data will be linked to HES data to determine COVID-19 related hospitalisations, and to the ONS death registry to determine COVID-19 related deaths. The association between ICS prescription and each outcome will be estimated using a Cox regression model to calculate hazard ratios and 95% confidence intervals, with confounding adjustment using multivariable regression and propensity scores. Subsequently, QBA will be used to account for potential sources of bias in these estimates of association, including exposure and outcome misclassification, residual confounding and selection bias.

This project will allow an evaluation of whether and how more widespread use of QBA might have allowed researchers to make better inferences using observational data about the role of ICS in COVID-19. Outputs from this project will provide recommendations and tools to help researchers implement QBA in pharmacoepidemiologic studies.

C. Background

ICS are anti-inflammatory drugs widely used as regular maintenance medications in asthma and chronic obstructive pulmonary disease (COPD). At the beginning of the COVID-19 pandemic, it was thought that people with asthma or COPD might be at higher risk of adverse COVID-19 related outcomes.[1,2] However, patients with asthma or COPD were not substantially overrepresented among COVID-19 deaths or hospitalisations.[3–5] It was not clear why, but it was suggested that lung disease, patients' behaviour or their treatment may have a protective effect.[5–8]

Several observational studies investigated the effects of ICS on COVID-19 outcomes but found inconsistent results that may be affected by biases.[9–13] A cohort study using the OpenSAFELY platform[9] found moderately increased risks for COVID-19-related mortality among people with asthma who using high-dose ICS (compared with short-acting beta-agonist only: adjusted hazard ratio (aHR) 1.55 (1.10–2.18)). No increased risk was found among people with asthma using low or medium-dose ICS (aHR 1.14 (0.85–1.54)). In the COPD cohort, an increased risk of death was found among people using ICS-long-acting beta-agonist (LABA) compared with those using LABA-long-acting muscarinic antagonists (LAMA) (aHR 1.39 (1.10–1.76)). E-values were used to estimate the association an unmeasured confounder would need to have with exposure or outcome to fully explain the result and showed that the observed harmful associations could plausibly be explained by confounding.[9] Bloom et al. found that among hospitalised people with COVID-19, patients over 50 years old with asthma using ICS had a reduced risk of death compared to people without respiratory disease (HR 0.86, 95% CI 0.80-0.92).[10] For younger patients with asthma (16-49 years), risk of death was significantly increased only for those with most severe asthma. Among those with COPD, both those with and without routine ICS use had an increased risk of death with COVID-19 compared to patients without respiratory disease (no ICS: HR 1.16, 95% CI 1.12−1.22; using ICS: HR 1.10, 95% CI 1.04−1.16).[10] A study using the Danish national registries found no statistically significant differences in COVID-19 outcomes between hospitalised patients routinely using ICS, patients using other inhaled pharmaceuticals (β_2-agonist and/or muscarinic receptor antagonists), and all patients without ICS use (30-day hazard of death of ICS users compared with users of other inhaled pharmaceuticals (HR 0.84, 95% CI 0.54-1.31)).[12] Aveyard et al. found that routine users of ICS were at modestly increased risk of severe COVID-19 outcomes adjusted for respiratory disease and other comorbidities (aHR for hospitalisation 1.13, 95% CI 1.03-1.23, aHR for death 1.15, 95% CI 1.01-1.31) compared to the general population not using ICS.[13]

Additionally, two randomised controlled trials (RCTs) have found beneficial effects of inhaled budesonide on recovery times in patients with symptomatic COVID-19[14,15], while RCTs investigating ciclesonide have found conflicting results, with one study finding shortened duration of viral shedding[16] and two studies finding no statistically significant effect of ciclesonide on symptom resolution on day 7[17] or time to symptom alleviation[18]. RCTs consequently suggested a strong protective effect of one inhaled ICS, budesonide, in patients with mild COVID-19.[14,15] The conflicting results between the RCTs and observational studies may be a result of different study questions and populations, or biases affecting the observational studies.

The design of pharmacoepidemiologic studies in COVID-19 is complicated by the polyphasic nature of the disease, which means that different treatments may have different effects at different stages of the COVID-19 disease pathway from infection to hospitalisation and death.[19] It can therefore be difficult to compare results between studies when there are differences in study design and differences in timing of drug administration, and the populations studied.[19] However, the inconsistent findings may also be in part due to biases affecting the studies.

QBA is a form of sensitivity analysis that aims to quantify and adjust for systematic errors and the uncertainty about these errors.[20] An important benefit of using QBA is that it makes assumptions regarding the structure and impact of the bias explicit and reduces overconfidence in research findings.[21–23] Despite having first been described decades ago.[22,24–26] QBA has so far rarely been applied to epidemiologic studies[26,27], which may in part be due to a lack of guidance on which methods to apply and how best to apply them.[20,28,29] QBA can be applied to many types of biases that may arise in pharmacoepidemiologic studies, such as exposure and outcome misclassification, selection bias and confounding. For example, misclassification of drug exposures may arise in EHRs due to stockpiling of medication, patients not filling prescriptions, non-adherence, or underascertainment of in-hospital medication use. Using COVID-19 infection as an outcome may be subject to misclassification due to non-random testing and limited testing availability. Non-random testing may result in selection bias where testing is a condition of entry into the study population. Selection bias may also arise in the form of collider bias if study populations have been restricted to people experiencing an event such as COVID-19 testing or hospitalisation.[30]

Confounding can occur as confounding by indication when clinical indication influences the exposure, i.e., treatment, and the outcome under investigation. While using an active comparator can reduce confounding by indication, there is no perfect active comparator in asthma or COPD, and the reasons for choosing a specific treatment regimen are not always known.

Studies investigating the impact of ICS on COVID-19 outcomes have so far given conflicting results. ICS may have different effects at different stages of the COVID-19 disease pathway from infection to hospitalisation and death. It can therefore be difficult to compare results between studies when there are differences in study design and differences in timing of drug administration, and the populations studied.[19] However, the inconsistent findings may also be in part due to biases affecting the studies, including for example bias due to imperfect and incomplete ascertainment of SARS-CoV-2 infections or misclassification of ICS exposures. This study will use ICS as a “case study” to investigate the application of QBA in pharmacoepidemiologic studies of COVID-19.

D. Aims, objectives, rationale

The aim of this study is to investigate the effects of ICS at different stages of the COVID-19 disease pathway (i.e., infection, hospitalisation, and death) among patients with asthma or COPD and apply methods of QBA to these effect estimates to account for potential biases arising in these estimates of association. The null hypothesis is that use of ICS has no effect on COVID-19-related outcomes.

Objectives

A. To describe prescription patterns of ICS among patients with respiratory diseases before and during the COVID-19 pandemic.
B. To investigate the association between prevalent ICS use and COVID-19 related outcomes among patients with respiratory diseases.
    a. Estimate the association between prevalent ICS use and risk of having a positive SARS-CoV-2 test.
    b. Estimate the association between prevalent ICS use and risk of hospitalization with COVID-19 among patients with a positive SARS-CoV-2 test.
    c. Estimate the association between prevalent ICS use and risk of death among patients who were hospitalized with COVID-19.
C. To develop approaches and apply methods of QBA to account for potential biases arising in these estimates of association.
    a. Investigate impact of exposure misclassification (e.g., due to stockpiling of medication, patients not filling prescription or underascertainment of in-hospital medication use) on estimates from objective 2a, 2b, and 2c.
    b. Quantify potential biases due to unmeasured or unknown confounders on estimates from objective 2a, 2b, and 2c.
    c. Investigate impact of outcome misclassification (e.g., underascertainment of infections due to limited testing availability and non-random testing) on estimates from objective 2a.
    d. Investigate impact of selection bias (e.g., non-random selection of individuals into a study) on estimates from objective 2b and 2c.

E. Outcomes

COVID-19 positive test result; hospitalisation with COVID-19; death with COVID-19, as defined in section N.

F. Study type

The overall study design is a historical cohort study.

G. Study design

Objective 1 will be a descriptive study with a population-level description of prescription patterns of ICS before and during the COVID-19 pandemic among patients with respiratory disease.

Objective 2 will be a hypothesis testing cohort study. The null hypothesis is that there is no association between ICS use and testing positive for COVID-19, hospitalisation for COVID-19 and death with COVID-19.

Objective 3 will be a methodological study to develop and apply methods of quantitative bias analysis to account for potential biases arising in the estimates of the effects of ICS on COVID-19 outcomes.

H. Data source

This project will use the Clinical Practice Research Datalink (CPRD) Aurum, a database containing routinely collected patient data from GPs in the UK. CPRD Aurum includes data on 41 million patients (March 2022), with over 13 million patients currently registered (20% of the UK population).[31] These patients come from over 1,300 GP practices which use EMIS GP patient management software.[31] CPRD records information on diagnoses, symptoms, demographics and lifestyle factors, prescriptions, referrals, vaccinations and tests[31,32], coded using SNOMED and Dictionary of Medicines and Devices (DM+D) codes. CPRD Aurum has been shown to be broadly representative of the English population in terms of age, gender, geographical spread and deprivation.[32]

I. Linked data

Data from CPRD can be linked to other databases such as the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) death registry. Both HES and ONS death registry data are linked to CPRD by NHS Digital using the NHS number, gender, date of birth and postcode.[32,33] HES holds information on all patient contacts at NHS hospitals in England, with diagnoses recorded using International Classification of Disease 10th revision (ICD-10) codes.[33,34] ONS death registry data contains information on all deaths occurring in England and Wales, including a cause of death documented using ICD-10 codes.[34,35]

HES Admitted Patient Care will be used to identify hospitalisation with COVID-19. ONS death registration data will be used to identify death with COVID-19. Additionally, the Index of Multiple Deprivation (IMD) will be used as a covariate to adjust for socioeconomic deprivation, which has been associated with COVID-19 outcomes.[36]

J. Feasibility counts

A feasibility count based on CPRD Aurum June 2021 build identified 225,472 patients with a COPD code before 29th February 2020, and 755,632 patients with an asthma code between 1st March 2017 and 29th February 2020. These patients were registered in CPRD on 1st March 2020 and had at least one year of registration prior to that date.

Furthermore, 1,031,882 patients who received a prescription for ICS between 01st March 2019 and 29th February 2020 were identified. Of the patients with asthma, 485,192 had a prescription for ICS. Of the patients with COPD, 83,668 had a prescription for ICS.

		With ICS prescription 01/03/2019-29/02/2020
Asthma	755,632	485,192 (64.2%)
COPD	225,472	83,668 (37.1%)

K. Sample size considerations

Between 01st March 2020 and 31st August 2020, 295,134 positive SARS-CoV-2 tests were reported in England.[37] Based on a population of 56,550,000[38], that corresponds to 0.52% of the population testing positive for SARS-CoV-2. During that time period, 36,974 deaths with COVID-19 occurred in England, corresponding to 0.065% of the population.

Table 1. Sample size calculations for α = 0.05 and 80% power, assuming 64% of the study population are prescribed ICS.

Outcome probability in controls	HR=1.1	HR=1.2	HR=1.3	HR=1.4	HR=1.5	HR=1.6	HR=1.7
0.05%	7,500,266	2,049,648	989,797	601,807	414,428	308,428	241,978
0.1%	3,750,133	1,024,824	494,899	300,904	207,214	154,214	120,989
0.2%	1,875,067	512,412	247,450	150,452	103,607	77,107	60,495
0.3%	1,250,045	341,608	164,967	100,302	69,072	51,405	40,330
0.4%	937,534	256,206	123,725	75,226	51,804	38,554	30,248
0.5%	750,027	204,965	98,980	60,181	41,443	30,843	24,198
0.6%	625,023	170,804	82,484	50,151	34,536	25,703	20,165
0.7%	535,734	146,404	70,700	42,987	29,602	22,031	17,285
0.8%	468,767	128,103	61,863	37,613	25,902	19,277	15,124
0.9%	416,682	113,870	54,989	33,434	23,024	17,135	13,444
1.0%	375,014	102,483	49,490	30,091	20,722	15,422	12,099

Assuming the probability of testing positive for SARS-CoV-2 among people with asthma or COPD is equal to or higher than the probability of testing positive among the general population, this study will likely be adequately powered to detect HRs of 1.1 or higher in the asthma population and 1.2 or higher in the COPD population for the outcome of testing positive. For the rarest outcome, death, the study would be powered to detect HRs higher than 1.4 in the asthma cohort and 1.7 in the COPD cohort.

L. Study population

Descriptive study

For the descriptive study, we will examine prescription patterns of ICS in two cohorts: patients with COPD and patients with asthma. Follow-up will be from 1st March 2019 until the end of wave 2 of COVID-19 in the UK (30th April 2021).

For each cohort and each calendar month, the study population will consist of people who have a record of asthma or COPD. For the asthma cohorts, each monthly cohort will consist of those patients who, on the 15th of each month (the index date), had 1) their first asthma code on or before that date; and 2) did not have COPD on or before that date.[39] Correspondingly, for the COPD cohorts, each monthly cohort will consist of those patients who, on the 15th of each month, had 1) their first COPD code on or before that date; and 2) did not have asthma on or within 3 years before that date. To be included in a cohort, patients must have at least one year of follow-up in CPRD prior to the index date and have age and gender recorded in CPRD.

Comparative cohort studies

For the comparative cohort studies, the study population will consist of two separate, mutually exclusive disease cohorts, a COPD cohort and an asthma cohort, consisting of patients registered with GP practices meeting CPRD quality control standards. For each disease cohort (asthma and COPD), two cohorts will be created, one for the first wave of COVID-19 and one for the second, defined relative to a cohort entry date (1st March 2020 for wave 1, 1st September 2020 for wave 2), to make a total of four cohorts. To be included in a cohort, patients must have at least one year of follow-up in CPRD prior to the cohort entry date, be eligible for linkage to HES data, and have gender and age recorded in CPRD.

Asthma cohort[40]

The asthma cohort will include all adults aged 18 and over with a recorded diagnosis of asthma defined as a record of asthma within 3 years prior to the cohort entry date. This method of identifying asthma has previously been validated in CPRD.[40] Code lists to identify asthma will be reviewed by a clinical expert before use.

Patients will be excluded if they have a record of COPD or any other chronic respiratory condition at any point before the cohort entry date, or a prescription of a LAMA but no ICS within 3 years before the cohort entry date, as this indicates possible COPD. Patients who received a prescription of nebulised medication within 1 year before the cohort entry date will also be excluded, as this indicates very severe asthma.

COPD cohort[41]

The COPD cohort will include all adults aged 35 and over with a recorded diagnosis of COPD at any point before the cohort entry date.[41] This method of identifying COPD has previously been validated in CPRD.[41] Code lists to identify COPD will be reviewed by a clinical expert before use. To be included, patients must also have a record of current or former smoking in CPRD.

As in the asthma cohort, patients who have a record of other chronic respiratory conditions at any point before the cohort entry date will be excluded. People who use a leukotriene receptor antagonist (LTRA) within 3 years of the cohort entry date will be excluded as this indicates asthma, as will people who are prescribed a LABA/LAMA and ICS within 3 months before the cohort entry date, as this indicates severe COPD.

Censoring

For all cohorts, cohort exit will be defined as the first of either occurrence of the outcome (for each analysis), death, disenrollment from GP practice, the last date of data availability, or the end of the COVID-19 wave (31st August 2020 for wave 1, 30th April 2021 for wave 2).

M. Comparator groups

The study will use an active comparator group including all people with recorded asthma within 3 years or COPD at any point before the cohort entry date (1st March 2020 or 1st September 2020, respectively) who received a prescription for inhaled medication for asthma or COPD, but no ICS prescription.

The comparator group for the asthma cohort will be people who were not prescribed medication containing ICS and were prescribed a non-ICS inhaled medication for asthma. For the COPD cohort, the comparator group will include people who were not prescribed a medication containing ICS and were prescribed a LABA/LAMA separately or in combination for COPD. Exposures and exposure durations in the comparator group will be calculated in the same way as in the ICS-exposed group.

N. Exposures, outcomes and covariates

Exposure

Exposure will be prescription of ICS, which may be determined in a time-fixed or time-updated manner. Which method of exposure ascertainment will be chosen will be informed by the findings of the descriptive study of prescription patterns. For example, if we observe a significant increase in prescriptions for ICS at the start of the pandemic (March 2020) in the descriptive study, suggesting stockpiling occurred, it may be difficult to ascertain the end of an exposure period. While a time-updated approach would be more accurate and preferable in theory, a time-fixed exposure definition may be preferable if exposure periods cannot be estimated with confidence, for example due to stockpiling. The descriptive study will be completed before the start of the analyses of the comparative studies.

- **Time-fixed exposure**: prescription of ICS within 3 months before the cohort entry date (1st March 2020 for wave 1, 1st September 2020 for wave 2), and the comparator group as people who did not receive a prescription for ICS within the 3 months before the cohort entry date, but did receive a prescription for another inhaled medication for COPD or asthma. Patients can then not switch between exposure groups, even if they initiate ICS or their ICS exposure ends, analogous to an “intention to treat” approach.
- **Time-updated exposure**: ICS prescriptions in the year before the cohort entry date up until the end of follow-up will be used to ascertain exposure status throughout the follow-up time. Length of exposure for each prescription will be calculated by multiplying the quantity by any relevant dose information stored in the packtype variable and dividing by the value in the numeric daily dose variable. Where it is not possible to calculate the exposure period, the median prescription length for that drug might be imputed as the exposure duration.[42] An allowable gap between the end of a calculated drug supply and receipt of a new prescription would be permitted, e.g. half a median exposure duration. Where one prescription is issued

before the previous one is estimated to have been completely used, we will assume stockpiling occurred and assign the maximum total days of exposure possible with the combined prescriptions. Patients who switch treatment groups will be considered exposed to the active comparator/ICS group from the date of the switch, and those who discontinue treatment or switch to a treatment not under study will be censored at discontinuation or switch.

Patients will be considered exposed from the date the prescription was issued, as ICS have been shown to exert anti-inflammatory effects within hours of administration.[43]

Outcomes

- SARS-CoV-2 infection, defined as a recorded positive test for SARS-CoV-2 in the primary care record sourced from the Second Generation Surveillance System (SGSS).
- hospitalisation with COVID-19, defined as admission to hospital with an ICD-10 code for COVID-19, ascertained using HES data.
- death with COVID-19, defined as death with an ICD-10 code for COVID-19 listed as an underlying or contributing cause of death in the ONS death registry.

Covariates

- demographic and lifestyle variables at baseline: age, sex, body mass index (BMI), smoking status, ethnicity, socioeconomic status (Index of Multiple Deprivation, IMD)
- ever-present comorbidities at baseline: chronic kidney disease, hypertension, heart failure, other heart diseases, diabetes, cancer, immunosuppression
- time-updated covariates: influenza vaccination within one year before the cohort entry date, pneumococcal vaccination within 5 years before the cohort entry date, vaccination against COVID-19 (wave 2 only)
- calendar time, COVID-19 prevalence figures (ONS)
- asthma cohort only: number of recorded asthma exacerbations (emergency department visit, hospitalisation or prescription of an oral corticosteroid for asthma[44]) within 1 year before the cohort entry date
- COPD cohort only: number of recorded COPD exacerbations (defined using a validated algorithm[45]) within 1 year before the cohort entry date.

O. Data analysis

Descriptive study:

Population-level measures of ICS use that will be determined per calendar month are:

- Number and proportion of incident and prevalent users over the course of follow-up for each calendar month:
    - Prevalent ICS exposure will include people with an ICS prescription recorded on any day during that month.

    - Incident ICS exposure will be defined as a new ICS prescription with no prescription in the previous 6 months. Prevalent users will therefore also include incident users.
    - The denominator will be all people with asthma or COPD in each month**Error! Reference source not found.**.
- Number of individual prescriptions per person per month (absolute number).
- Dosages prescribed: median or mean daily dose among those prescribed ICS for any given month.
- Discontinuation of ICS or date of treatment switch: number and proportion of people who have ≥6 months of no ICS-containing inhaler prescription.

This study will be descriptive. Results will be presented as absolute numbers and proportions as bar graphs.

The results from this study will inform the exposure definition that will be used in the comparative cohort study (see section on Exposure definitions). This study will be completed before starting the analyses for the subsequent comparative cohort studies.

Comparative cohort studies:

We will conduct descriptive analyses (frequency, percentages, mean [SD] and median [IQR]) to assess characteristics of the patients in each cohort, stratified by exposure group at baseline. Categorical variables will be compared using χ^2 tests. Continuous variables will be compared using t-tests for normally distributed variables and Mann-Whitney test for non-normally distributed variables. Time to each outcome will be presented using Kaplan-Meier plots using time in study as the time scale.

Propensity scores will be generated using logistic regression to estimate likelihood of ICS prescription based on baseline characteristics. All pre-specified covariates will be included in the logistic regression.

The association between ICS prescription and each outcome will be estimated using a Cox regression model to calculate hazard ratios and 95% CIs, using time in study as the time scale. Univariable models, models adjusted for age and sex, and propensity score weighted models will be presented. Schoenfeld residuals will be used to graphically assess the validity of the proportional hazards assumption. If the proportional hazards assumption is violated, we will use interaction terms between the exposure and time to describe any variations in the hazard ratio over time.

If a time-updated exposure definition is used, we will account for potentially informative censoring using inverse-probability of censoring weights. Propensity scores will also be time-updated to account for time-dependent confounding.

A number of sensitivity analyses/additional analyses will be conducted:

    - Stratification by ICS dose (low/medium vs higher)
    - Do not condition on positive test (2b) or hospitalisation (2c), in order to repeat published analyses

- Include people with a diagnostic code for COVID-19, or a code that implied SARS-CoV-2 infection, but no registered positive SARS-CoV-2 test

P. Quantitative Bias Analysis

Quantitative Bias Analysis Method:

We will use probabilistic bias analysis to quantify the effect of biases on the effect estimates in objectives 2a-c. In probabilistic bias analysis, each bias parameter is assigned a distribution which reflects the uncertainty around the specific value for the parameter. The bias parameters are sampled repeatedly from this distribution and applied to the observed effect measure to obtain a bias-adjusted point estimate and simulation interval.[22,46] For research questions where more than one bias may have a significant impact, we will also conduct multiple bias modelling to obtain effect estimates that are adjusted for several biases.

Misclassification:

We will use a range of plausible values for sensitivity and specificity of the outcome and exposure classification to adjust for outcome and exposure misclassification, respectively.

Exposure misclassification may arise due to low adherence to inhaled medication for respiratory diseases[47–49], and due to stockpiling of medication at the beginning of the pandemic (March and April 2020). The descriptive cohort study (objective 1) will investigate prescription patterns and the potential extent of stockpiling during the pandemic. To adjust for potential exposure misclassification, we will calculate proxy measures for adherence (proportion of days covered or medication possession ratio) in the year before the COVID-19 pandemic (March 2019 – February 2020) and use these, together with data from literature and input from clinicians, to estimate adherence during the pandemic. Additionally, we are looking to obtain questionnaire data on adherence during the pandemic from the Optimum Patient Care Research Database (OPCRD). If this data is not obtained, or is not suitable for these purposes, we will estimate exposure misclassification using data from literature and input from clinicians.

In objective 2a, the outcome of SARS-CoV-2 infection may be misclassified as testing was conducted in a non-random manner. Especially in the first wave of COVID-19, testing was very limited, and therefore not all infections will have been ascertained. It is plausible that the probability of getting tested for SARS-CoV-2 was not equal among people prescribed ICS and those not prescribed ICS, resulting in differential misclassification of SARS-CoV-2 infection. We will use test data from CPRD and data from the ONS infection survey to estimate how many SARS-CoV-2 infections may have been missed in the respective study populations. We will work together with clinicians to create plausible bounds for sensitivity and specificity of the outcome classification.

Selection Bias:

Analyses that are restricted to people who received a positive test for SARS-CoV-2 or were hospitalised with COVID-19 may be vulnerable to selection bias. Potential differential misclassification of SARS-CoV-2 infections in objective 2a would result in selection bias in objective 2b, as selection into the study

population is conditional on a positive test for SARS-CoV-2. In order to adjust for selection bias, the bias parameters necessary are the selection probabilities S for each combination of exposure E and outcome D:

- Probability of being selected into the study conditional on being exposed and experiencing the outcome (P(S|D=1, E=1)),
- Probability of being selected conditional on being exposed and not experiencing the outcome (P(S|D=0, E=1)),
- Probability of being selected conditional on being unexposed and experiencing the outcome (P(S|D=1, E=0)),
- Probability of being selected conditional on being unexposed and not experiencing the outcome (P(S|D=0, E=0)).

The observed effect estimate can then be multiplied with the OR for differential selection to give an effect estimate adjusted for differential selection into the study population. To estimate the impact of possible selection bias affecting effect estimates in objective 2b, we will use information relating to the underascertainment of SARS-CoV-2 infections, described above. To account for selection bias in objective 2c, we will use HES data, together with data on ICS exposure from CPRD and data on the outcome, death with COVID-19, from the ONS death registry, to determine probabilities for being selected into the study population (i.e., being hospitalised with COVID-19) for each combination of exposure and outcome.

Confounding:

We expect that there will be unmeasured confounding affecting the effect estimates in objectives 2a-c. A likely key source of unmeasured confounding may be the severity of the underlying respiratory disease. It has not been elucidated completely how asthma and COPD affect COVID-19 outcomes[7,50–55], but it is plausible that severity of respiratory disease influenced COVID-19 outcomes and that people using ICS had a different severity of underlying respiratory disease than those not prescribed ICS. Any observed effect of ICS on COVID-19 outcomes may then be partly due to different severity of respiratory disease between the exposed and unexposed. We will account for unmeasured confounding by respiratory disease severity using an estimate of the association between severe respiratory disease and the outcome among the unexposed, an estimate of the association between severe respiratory disease and ICS exposure, and the prevalence of severe respiratory disease among the source population.[23,56] We will work together with clinicians to develop an algorithm to identify severe respiratory disease in CPRD and/or estimate plausible bounds.

Q. Plans for addressing confounding

The distribution of confounders will be compared descriptively between users and non-users of ICS. We will use multivariable regression, and propensity scores where appropriate, to adjust for confounding. Covariates used to estimate the propensity score will be selected based on literature and are listed in section N. If a time-updated exposure definition is used, we will generate time-updated confounders.

We will use quantitative bias analysis to quantify the extent to which unmeasured confounding could bias our studies.

R. Missing data

We expect some missing covariate information for BMI, smoking status, and ethnicity. Missing data on ethnicity will be supplemented using HES data.[57] The characteristics of individuals with and without missing data will be compared to identify systematic differences which may bias the results. The primary analysis will be conducted excluding variables with a considerable number of missing values (>10%). We will consider using multiple imputation or complete records analysis for variables that may be important confounders, depending on the degree of missingness.

S. Patient and user group involvement

We are exploring ways to obtain patient input to contextualise the experiences of people with asthma or COPD during the pandemic, in particular how they may have used or stockpiled prescriptions of ICS in waves 1 and 2.

T. Limitations

An aim of this project is to address some of the limitations of observational research using QBA. Many of the limitations that may affect this study of ICS and COVID-19 outcomes, such as incomplete ascertainment of SARS-CoV-2 infections, unmeasured confounding, and collider bias, will be addressed using QBA. The source and uncertainty about the bias parameters may not always be known and will likely involve a combination of extrapolation from published literature, estimates from other studies, and detailed discussion with a respiratory clinician. For this reason, we will explore a range of values for each bias parameter.

The data source has some missing covariate information. We will exclude covariates with large amounts of missing values from the primary analysis and will consider conducting a sensitivity analysis including those variables using multiple imputation or complete records analysis, depending on the degree of missingness. Furthermore, quantitative bias analysis will be used to assess the extent to which unmeasured confounders may impact study results.

An additional limitation is that the study may be underpowered to detect small effects (HRs <1.2) if the outcome is very rare (<0.5%).

U. Plans for dissemination and communication of study results

Results will be presented at conferences (e.g. ICPE, SER) and submitted for publication in peer-reviewed journals (e.g. Lancet Respir. Med, Pharmacoepidemiology and Drug Safety).

V. Data Storage and Security

The data will be stored on a secure data server, within the London School of Hygiene and Tropical Medicine network. Access will be restricted to named users with specific involvement in the project.

The analysis dataset including those variables (exposures, outcomes, covariates) justified in the protocol and used for the analysis as outlined in the protocol will be archived on an Electronic Health Records Research Group drive on the LSHTM school network.

Data will remain on the secure server for the duration of the project, or until the end of the data retention period stipulated by the data owners. After this time, all data will be destroyed following the CPRD guidelines using dedicated software.

Analysis code will be uploaded on GitHub.

W. Ethics approvals

The data used in this project are routinely collected and anonymised data from the Clinical Practice Research Datalink (CPRD). The CPRD Group has in place ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data; namely, studies which do not include patient involvement (including this study, see https://www.cprd.com/content/guidance-completion-cprd-research-data-governance-rdg-application).

The current project (which does not include patient involvement) does fall within the overall scope of existing CPRD approvals. However, all projects using CPRD data have to obtain additional approval from the CPRD Research Data Governance (RDG). CPRD RDG committees review protocols for feasibility, public health benefits/risks and information governance risks. A scientific proposal has been submitted to the CPRD RDG and approved by CPRD Research Data Governance (CPRD reference 22_001876).

Additionally, the project has been approved by London School of Hygiene and Tropical Medicine Ethics Committee (Project ID: 27896).

X. Expected timelines

Start of funding: 19/04/2021

Registration in EU PAS register: 11/07/2022

Start of data collection/extraction: 01/09/2022

Start of data management: 01/09/2022

Start of data analysis: 02/01/2023

Final study report: 31/10/2024

Y. Conflicts of Interest

MB is funded by a GlaxoSmithKline PhD studentship to investigate the application of quantitative bias analysis in observational studies of COVID-19. ID has unrestricted grants from and shares in GSK. AS is employed by LSHTM on a fellowship sponsored by GSK. JH is employed by GSK and owns stock in GSK. CTR and JQ report no conflicts of interest.

Z. References

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AA. Amendments